

POSTER PRESENTATION

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Tauopathy-induced retinal dysfunction in the P301S mutant human tau transgenic mouse

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Intracellular inclusions made of microtubule-associated tau protein are a defining pathological hallmark of tauopathies, which include Alzheimer disease and familial frontotemporal dementia and parkinsonism linked to chromosome 17. Altered levels of tau protein have been detected in the retina and optic nerve of patients with glaucoma, suggesting that retina degeneration and tauopathies share similar pathogenic mechanisms. We have recently demonstrated that P301S mutant human tau (τ_{P301S}) mice develop tau filamentous inclusions and axonopathy in retinal ganglion neurons (RGCs), in the absence of neuronal loss or alterations in the outer retina. Moreover, we showed that τ_{P301S} transgenic retinal explants do not respond to neurotrophic stimuli *in vitro*. Here, we investigated the impact of tau pathology on RGC physiology in living animals and neurotrophin signaling pathways *in vivo*. In anesthetized 5-month old wild type (WT) and τ_{P301S} mice, we measured RGCs activity using pattern electroretinogram (pERG), which selectively detects RGC response upon pattern light stimuli exposure. In transgenic τ_{P301S} mice the amplitude of both P1 positive and N2 negative components of pERG at saturating contrast and spatial frequency was significantly smaller than WT values. Furthermore, retinal acuity was significantly reduced in τ_{P301S} mice. Using uniform flickers of light (flash ERG), we measured the activity of the outer retina and found that outer retina response was preserved in τ_{P301S} mice. Neurotrophins, and especially brain-derived neurotrophic factor (BDNF), are important modulators of neuronal survival and function in the brain and in the visual system. We therefore investigated the BDNF signaling pathway and found that BDNF signalling was altered in τ_{P301S} transgenic retinas. Our

results indicate that, in the τ_{P301S} mouse, tau pathology specifically impairs the activity of RGCs, without affecting the outer retina function and is associated with BDNF signalling alterations. Given the role of BDNF in synaptic plasticity, these data suggest that mild levels of tau pathology are sufficient to trigger significant neuronal dysfunction possibly through alteration of neurotrophic signalling. *Funded by a grant of Compagnia di San Paolo awarded to LG.*

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